Double Trouble Myotonic Dystrophy Type-1 and Parkinson Syndrome Associated with Variants in *SYNJI, VPS13C*, and *DNAJC6*

We read with interest the article by Misra *et al*.[1] who reported on a 45-year-old female who developed progressive spastic quadriparesis with proximal predominance since the age of 40 and Parkinson syndrome since the age of 42. Genetic testing by TP-PCR revealed a CTG-repeat expansion of >50 repeats in the *DMPK* gene.[1] Whole exome sequencing (WES) revealed variants in *SYNJI, VPS13C*, and *DNAJC6*.[1] She was diagnosed with myotonic dystrophy type-1 (MD1) and Parkinson syndrome.[1] L-DOPA had only a minimal effect.[1] The study is compelling but has limitations that should be discussed.

A major limitation of the study is that the exact number of triplet repeats was not reported. Figure 1 in Misra's article only shows that the CTG-repeat number on one allele was >50 but does not specify the exact amount. Furthermore, the three variants reported could be variants of uncertain significance (VUS) being potentially damaging on various in-silica prediction models such as Polyphen-2, SIFT, and Mutation Taster without guaranteed pathogenicity. Data on the familial segregation of these variants could have shed more light on the matter.

We disagree with the notion that Parkinson syndrome was reported in only eight patients so far as indicated in Table 2 of Misra's study.[1] According to a Pubmed search until the end of May 2023 at least two more cases of MD1 with Parkinson syndrome were reported.[2] A further argument for a higher prevalence of Parkinson syndrome as a phenotypic feature of MD1 is that in an autopsy study of 32 cases with MD1, one-third had Lewy pathology on brain autopsy.[3]

There is a discrepancy between the statement that there was quadriparesis with proximal predominance and the statement that muscle force in small hand muscles was normal.[1] This discrepancy requires clarification.

There is also a discrepancy between the fact that the patient had quadriparesis and normal creatine kinase. Quadriparesis suggests that the patient had myopathy. Myopathy in MD1 is usually associated with at least mild creatine-kinase elevation.

Another limitation of the study is that no family history was reported. We should know whether or not MD1 was inherited and whether or not any of the patient's first-degree relatives had Parkinson syndrome.

MD1 commonly manifests phenotypically with early cataract but the results of ophthalmologic investigations were not provided. We should be informed whether or not slit lamp investigations were indicative of cataract.

A typical phenotypic feature of MD1 is "myopathic face," which is characterized by frontal baldness, ptosis, hypomimia, atrophy of facialis innervated muscles, and open mouth.[4] We should know if the index patient had myopathic face due to MD1, hypomimia due to Parkinson disease or both.

A common early phenotypic manifestation of MD1 is atrio-ventricular block-1.[4] We should know whether or not the PQ interval was prolonged >20ms on electrocardiography (ECG) and what caused sinusbradycardia. We should also be informed about the results of echocardiography and whether or not proBNP and troponin were within normal ranges.

Speaking in a low voice (hypophonia) not necessarily means Parkinson syndrome.[1] Hypophonia is also a known manifestation of MD1.[5]

The authors should also explain why "pallidal hypometabolism" in FDG-PET has been given such importance. TRODAT should be essential in such cases, not FDG-PET. Whether FDG-PET has any relevance or clinical implication in such a scenario should be explained.

In summary, the interesting study has limitations that put the results and their interpretation into perspective. Addressing these issues would strengthen the conclusions and could improve the status of the study. Since the index patient not only carried a CTG-repeat expansion but also pathogenic variants in genes associated with hereditary Parkinson syndrome,[6] it is more likely that Parkinson syndrome was due to these variants than a phenotypic feature of MD1.

Acknowledgements

Statement of Ethics: a) The study was approved by the institutional review board. b) Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Data availability statement: data that support the findings of the study are available from the corresponding author.

Author contribution: JF: design, literature search, discussion, first draft, critical comments, final approval.

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Conflicts of interest

There are no conflicts of interest.

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